REMARKS

Claims 1-11 are currently pending in the application. Claim 4 is withdrawn. Claims 1 and 3 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

The specification has been amended to delete the Abstract on page 976. The Abstract on page 201 is the correct Abstract.

Claim Objections

The Office Action states that claims 1-3 and 5-11 are objected to on the grounds that the recitation, "a second amino acid sequence comprising a ligand for a cell surface polypeptide of a leukocyte," is awkwardly presented. The Office Action suggests amendment to, "a second amino acid sequence comprising the amino acid sequence of a ligand for a cell surface polypeptide of a leukocyte."

The claim is intended to limit the second amino acid sequence to being capable of binding to the recited cell surface polypeptide (whether or not the entire second amino acid sequence is required for such binding). Applicants are uncertain as to how the proposed amendment renders the claim language less awkward. Applicants respectfully request further explanation from Examiner regarding this language. Pending such explanation and/or discussion, Applicants respectfully maintain the language as originally entered.

The Office Action states that claims 6 and 7 are objected to under 37 CFR 1.75(c) on the grounds that they fail to further limit the subject matter of a previous claim. Applicants respectfully disagree. As the Office Action states, claim 5, the dominant claim, is limited to certain types of antigen bearing target. These types of antigen bearing targets encompass pathogenic and non-pathogenic entities, and each of these types of antigen bearing targets can be attenuated or can be left unattenuated. Accordingly, claims 6 and 7 further limit claim 5 by requiring that the antigen bearing target recited in claim 5 be, additionally, pathogenic or attenuated, respectively. Applicants therefore request that the objection be withdrawn.

Rejection of Claims 1-3 and 5-11 Under 35 U.S.C. §112, Second Paragraph

The Office Action states that claims 1-3 and 5-13 are rejected for indefiniteness under 35 U.S.C. §112, second paragraph. The Office Action states that the word "some" renders the claims indefinite. Applicants traverse the rejection, since they submit that the claims clearly read on compositions in which any amount of the recited fusion polypeptide is not bound to the recited cell or virus. In the interest of expediting prosecution, though, Applicants are herewith amending the cited claims to remove the phrase "some of".

The Office Action also states that claim 3 is rejected on the grounds that the recitation "at least about", particularly the word "about", renders the claim indefinite. Applicants respectfully disagree. Nevertheless, in order to expedite prosecution, Applicants are herewith amending claim 3 to remove the word "about".

Rejection of Claims 1-3 and 5-11 Under 35 U.S.C. §112, First Paragraph

Written Description

The Office Action states that claims 1-3 and 5-11 are rejected under 35 U.S.C. §112 on the grounds that they fail to comply with the written description requirement. The Office Action states, "It is recognized that the fusion protein acts as an adjuvant in the claimed vaccine composition, and the cell is the active ingredient that provides protective immunity against a disease.... Thus, the claimed invention is directed at a broad genus of vaccines that provide protection...."

These statements made in the Office Action import limitations that are not set forth in the claims, and such importation is not permissible. The invention, i.e. what is *claimed*, imposes no limitations on the fusion protein with respect to adjuvant function. Furthermore, it imposes no limitations on the antigen bearing target with respect to being the active ingredient that provides protection.

The instant claims, i.e. a vaccine composition, are not defined by the ability of the vaccine composition to provide "protection". It is defined by having composition and form that

make it *suitable for administration* to a subject, e.g. as taught in the specification under "Dosage and Administration" (paragraph 0536 and following). Again, Applicants submit that the relevant statements in the Office Action import limitations into what is claimed, and that such importation is not permitted. Furthermore, "vaccination" need not refer to "protection", but may refer to eliciting heightened immune responsiveness. This is supported by Dorland's Illustrated Medical Dictionary (1985, 26th Ed., W.B. Saunders Co., Philadelphia), which defines "vaccinate" as "to inoculate with a vaccine for the purpose of producing immunity", and further defines "immunity" as "heightened responsiveness to antigenic challenge that leads to more rapid binding or elimination of antigen than in the nonimmune state". Thus, to require that a vaccine composition of the invention provide "protection" is overly limiting. The vaccine compositions of the invention are not required to provide full protection, but would be understood by one of ordinary skill in the art to merely provide a heightened immune response, as defined above.

The Office Action further states that the specification discloses only two specific cells as having the ability to provide protective immunity against a disease, infection, and/or certain non-desired condition, i.e. irradiated CMS-5 and B16F10 cells. This statement imputes a requirement on what is claimed, i.e. an *outcome of* administration, that is not delimited in the claims. What is claimed is a type of composition with form and components that make it suitable for administration.

The Office Action states that the specification provides a "generic" list of cells that can be used in the invention. Applicants recognize that this may be intended as a criticism. Ironically, though, the adjective "generic" means of or pertaining to a genus. The Office Action therefore seems to acknowledge that the instant specification does describe the genus.

Applicants respectfully submit that the specification discloses various types of cells (see, for example, paragraphs 0480-0484). The specification also teaches multiple tumor types, from which cells can be obtained (paragraph 0549). Nevertheless, the Office Action states that only two "specific" cells are disclosed, i.e., B16 and CMS-5 cells. It is unclear to Applicants where the line is drawn as to what a "specific" cell is, and how CMS-5 and B16F10 cells are more "specific" than other cell types disclosed, e.g., keratinocytes. The key question is whether one

skilled in the art can discern possession of the genus "cell" from the disclosure, and Applicants respectfully submit that the answer is clearly "yes".

Furthermore, those of ordinary skill in the art understand *prima facie* what is meant by a "cell", and routinely discern which compositions comprise or do not comprise cells. Reference to a generalized cell is conventional and useful in the art, and limitation thereby in no way impairs the written description provided by the instant claims and specification. One skilled in the art will easily understand the meaning of the term "cell" and recognize the metes and bounds of what is claimed, and perceive that Applicants were in full possession of the invention at the time of filing.

The Office Action also states, "...it is gathered that the physical propert[y] required for cells that protect mice against tumor growth is irradiated tumor cells...." As discussed above, "protection" is not a limitation of what is claimed. In addition, Applicants respectfully submit that "irradiated tumor cells" are not at all required by the invention, i.e. what is claimed. Tumor cells are but one type of cell, and irradiation is one method of attenuation.

The Office Action further states that, under the written description requirement, "The full compound is required," citing *Fiers v. Revel* and *Amgen v. Chugai*. Applicants respectfully submit that the cited cases dealt with subject matter and issues that are fundamentally different from those of the instant invention. Specifically, the claims at issue in both cited cases were aimed at DNA molecules, the sequences of which were entirely unknown to man and which were not disclosed in the relevant specifications. In both cases, the DNA molecules themselves were claimed on the basis of encoding a given, complete polypeptide (human fibroblast beta interferon and human erythropoietin, respectively), even though the sequences of any such DNA's were not taught in the specifications and were unpublished by anyone at the time of filing. In other words, the DNA molecules were claimed in the absence of knowledge regarding their own, actual physical or chemical identities or properties, and in the absence of any established practice, principle, or utility in the art of treating the various potential species as a class.

Applicants submit that the subject matter now at issue, i.e. a cell, differs in at least two important ways from that of *Fiers* and *Amgen*. First, the structures and identities of cells are well

known to those skilled in the art. Second, as discussed above, textbooks and manuals are filled with principles, observations, and methods that relate to "cells", without regard to their origin or particular identity, so reference to a generalized cell is conventional and of great utility in the art. Applicants further respectfully reprise that the specification does disclose numerous types of cells. Thus, unlike the claims at bar in *Fiers* and *Amgen*, the instant claims are not drawn to a genus of unknown compounds, but instead relate to a novel and non-obvious combination of components that are possessed by those of skill in the art.

The Office Action also states that claim 3 is rejected under 35 U.S.C. §112 on the grounds that it fails to comply with the written description requirement. In particular, the Office Action objects to the recited limitation that the second amino acid sequence comprise at least five contiguous amino acids of a naturally occurring GM-CSF. The Office Action states that this limitation is directed at a genus, and further states that Applicants fail to provide adequate written description of the genus by providing sufficient description of a representative number of species. Applicants traverse the rejection.

First, Applicants note that the Office Action states, "... the cytokine is the active component that provides the adjuvant activity. Thus, the claim is drawn encompass second amino acid sequence having at least five contiguous amino acids of a naturally occurring GM-CSF, and function as an adjuvant."

This statement imputes function to the second amino acid sequence that is not a requirement of the invention, i.e. what is claimed. Indeed, Applicants submit that it is the entire multifunctional molecule of the invention that is responsible for any improved and unexpected "adjuvant" effect. The latter point aside, though, the second amino acid sequence is defined in the claim **not** by any self-contained adjuvant activity, but rather by the ability to bind to a cell surface polypeptide of a leukocyte, as recited in dominant claim 1. The rejection set out in the Office Action relies on an imputed requirement for adjuvant activity in the second amino acid sequence itself; this is not a proper basis for rejection.

The Office Action states that the specification does not provide the complete structure of naturally occurring GM-CSF. In fact, the specification provides references that teach the full amino acid sequence of GM-CSF (see paragraph 0155).

Furthermore, the specification teaches that the second amino acid sequence preferably includes at least five contiguous amino acids of a cytokine (see paragraph 0008), and more specifically teaches the preferred embodiment wherein the second amino acid sequence comprises at least five contiguous amino acids of naturally occurring GM-CSF (see paragraph 0051).

The Office Action acknowledges that adequate written description can rest on disclosure of relevant identifying characteristics, and sets forth a number of specific means by which this approach can be perfected. For example, the Office Action states that the written description requirement can be satisfied by delineation of physical and/or chemical properties and functional characteristics. Applicants agree that such criteria can fulfill the written description requirement.

In fact, there is a key functional and physical/chemical limitation in the claims that derives from the description in the specification. That is, that the second amino acid sequence must be a ligand for a cell surface polypeptide of a leukocyte. Applicants further note that there is extensive and well-known information in the literature regarding which amino acids of GM-CSF molecules are necessary, and which are not necessary for receptor binding and/or bioactivity. See, for example, Shanafelt et al., 1991, J. Biol. Chem. 266: 13804; Shanafelt and Kastelein, 1989, PNAS 86: 4872; Hercus et al., 1994, Blood 83:3500; Altman and Kastelein, 1995, J. Biol. Chem. 270: 2233; Monfardini et al., 1996, J. Biol. Chem. 271: 2966; Lopez et al., 1992 EMBO 11: 909; Meropol et al., 1992 J. Biol. Chem. 267: 14266; Schanafelt and Kastelein, 1992 J. Biol. Chem., 267: 25466; Seelig et al., 1994, J. Biol. Chem. 269: 5548; Shanafelt et al., 1991, EMBO 10: 4105 (Exhibits A-J, respectively). Thus, one of ordinary skill in the art would easily discern many members of a genus from the disclosures of the instant specification, and would recognize that the inventors were, correspondingly, in possession of many such members.

The Office Action further states that, under the written description requirement, "The full compound is required," citing *Fiers v. Revel* and *Amgen v. Chugai*. Applicants respectfully

submit that the cited cases dealt with subject matter and issues that are fundamentally different from those of the instant invention. Specifically, the claims at issue in both cited cases were aimed at DNA molecules, the sequences of which were entirely unknown to man and which were not disclosed in the relevant specifications. In both cases, the DNA molecules themselves were claimed on the basis of encoding a given, complete polypeptide (human fibroblast beta interferon and human erythropoietin, respectively), even though the sequences of any such DNA's were not taught in the specifications and were unpublished by anyone at the time of filing. In other words, the DNA molecules were claimed in the absence of knowledge regarding their own, actual physical or chemical identities or properties.

The subject matter now at issue, i.e. the amino acid sequence comprising at least five contiguous amino acid molecules of naturally occurring GM-CSF, differs in at least two important ways from that of *Fiers* and *Amgen*. First, the amino acid sequences of GM-CSF are well-known in the art and are, indeed, provided by reference in the instant specification. Second, the invention, i.e. what is claimed, is further defined by the fact that the "second amino acid sequence" can bind to a cell surface polypeptide of a leukocyte. Thus, unlike the claims of *Fiers* and *Amgen*, the instant claims define the metes and bounds of the claim element by its own structural and physical/chemical properties.

In addition, Applicants note that they were in full possession of the claimed invention at the time the application was filed. The species described fully embody all elements of the invention as claimed, and the specification therefore clearly conveys possession of the claimed invention to one skilled in the art. Applicants further note that the limitation regarding "at least five contiguous amino acids" is meant to exclude compositions failing to meet this standard, and that anyone reasonably skilled in the art could easily discern whether, on that basis, a given method fell within or without the potential purview of the claims in this regard.

Enablement

The Office Action also states that claims 1-11 are rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification is not enabling for the full scope of the claimed invention. The Office Action states that the specification is enabling only for vaccine

compositions in which the cells are CMS-5 or B16F10 tumor cells. Applicants disagree and respectfully traverse the rejection.

Applicants submit that what is claimed, i.e. a vaccine composition, is not defined by its ability to provide "protection". It is defined by having composition and form that make it *suitable for administration* to a subject, e.g. as taught in the specification under "Dosage and Administration" (paragraph 0536 and following). In addition, as noted above, to require that a vaccine provide "protection" is overly limiting, and the claims relate to compositions that provide a heightened immune response. As noted by the Office Action, the specification provides several working examples, utilizing different cell types, that demonstrate the ability of the claimed vaccine compositions to provide a heightened immune response. In addition, Applicants are filing herewith a declaration by Andrew Segal under 37 C.F.R. §132, that shows three additional cell types that can be used in vaccine compositions as claimed, and which provide a heightened immune response. Given the teachings in the specification, the working examples provided, and the subsequent data obtained following the teachings of the specification, one of skill in the art would appreciate that the claimed vaccine composition could be made and used in conjunction with the full scope of antigen bearing targets claimed.

Applicants further submit, without agreeing that enablement of the instant invention should stand on any outcome of administration, that heightened immune responsiveness is more reproducibly achieved across a range of antigens than protection from disease, particularly since the basic mechanisms governing antigen processing and presentation are independent of the origin of the antigen. The latter depends on interactions between the immune system and the harmful agent. The immune response *per se*, though, arises from similar processes, e.g. processing by antigen presenting cells and activation of lymphocytes, for a broad range of antigens. Accordingly, as discussed above, textbooks and manuals are filled with principles, observations, and methods that relate to "antigens", without regard to their origin or particular identity, so reference to a generalized antigen is conventional and of great utility in the art. Moreover, as actually defined in the specification, an "antigen" is "a molecule against which a subject can initiate a humoral and/or cellular immune response" (paragraph 0006).

The Office Action also states that "the specification only teaches of two vaccine compositions". To the contrary, the specification discloses a large number of antigens (see paragraphs 0436-0449), as well as various types of cells (see, for example, paragraphs 0482-0484, 0549) that can be incorporated into the claimed vaccine compositions. In addition, throughout the specification are taught a wide range of fusion proteins that may be used to meet the limitations of the claimed invention. The specification also teaches other components that may be included in the vaccine compositions (paragraph 0539 and following). In addition, Applicants are filing herewith a Rule 132 declaration by Andrew Segal showing additional working examples of the claimed invention.

The Office Action also cites Yu et al and Berzofsky et al with respect to "the complexities that hinder or defer the development of a cancer vaccine". The Office Action particularly refers to standards of reliably increasing patient survival or inducing tumor destruction. Such outcomes are not limitations of what is claimed. As discussed above, the claimed compositions are defined by what they comprise and by the fact that they are formulated for administration to a subject, and thus are fully enabled by the specification.

Without agreeing that enablement of the instant invention should stand on any outcome of administration, Applicants disagree that the specification fails to teach how to activate antitumor T cells. In fact, the specification teaches how to formulate and administer the claimed vaccine compositions, and further teaches the elicitation of T cells by such administration (see, e.g., paragraphs 0012, 0026, 0007, 0502, and the methods described in paragraphs 0509-0513, 0518, and 0538). Moreover, the Rule 132 declaration filed by Applicants herewith demonstrates that, by following the teachings of the specification, an antitumor T cell response is indeed elicited.

The Office Action also states that Berzofsky teaches that "the skilled artisan must find" antigens that clearly mark the tumor cells as different from the host cells. In fact, the reference teaches that this limits the number of antigens available. Berzofsky further teaches that related to this is additional potential challenge that, "Many potential tumor antigens are not expressed on the surface of tumor cells and thus are inaccessible *to antibodies*." (Emphasis added).

In fact, in the paragraph following these statements, Berzofsky et al teaches that, "The immune system has evolved a solution to this problem....", and goes on to describe the importance of MHC molecules. These molecules sample all proteins synthesized in the cell and present them to T cells. T cells are known to generally be unlikely to attack cells that only express proteins that are normally present in the host, making damage to normal cells unlikely; at the same time, they are able to recognize a wide range of antigens that are not normally in the host, e.g. tumor antigens, and attack cells that express them. Berzofsky further teaches that, unlike antibodies, which may not be important for tumor vaccines, T cells (e.g. cytotoxic T cells) are not limited to tumor antigens expressed intact on the cell surface but can detect any abnormal protein synthesized in the cell, greatly expanding the range of tumor antigens detectable by the immune system.

Applicants also note that the instant invention allows the practitioner to circumvent the need to identify any specific antigen at all, since it encompasses the use of whole cells, which *de facto* comprise all of the potential tumor antigens in the cells.

Applicants further note, again without agreeing that enablement of the instant invention should stand on any outcome of administration, that Berzofsky et al teaches a number of successes in the area of cancer vaccines, including cell-based vaccines. For example, it teaches that, "Tumor cells engineered to secrete a number of different cytokines have been shown to protect mice from challenge with the same tumor type." It further teaches that that the administration of tumor cells expressing GM-CSF resulted in one partial response in 21 melanoma patients, and that extensive inflammatory infiltrate with necrosis and fibrosis of tumor was seen in 11 of 16 melanoma patients biopsied. In another phase I trial, among 14 patients vaccinated with GM-CSF–transduced allogeneic pancreatic cancer cell lines after surgery, three patients remained disease free at 23 months. Furthermore, far from being daunted by the current state of the art, Berzofsky et al teaches that, "Increased understanding of the immune system has led to novel second-generation vaccine approaches that hold promise to control or cure cancer."

In further support of the rejection, the Office Action cites *In re Wright*. The principal claim at issue in this case was:

> A live, nonpathogenic vaccine for a pathogenic RNA virus comprising an immunologically effective amount of a viral antigenic genomic expression having an antigenic determinant region of the RNA virus but no pathogenic properties.

There are fundamental differences between the claims of *In re Wright* and those of the instant invention. First, the former has as a limitation the phrase "immunologically effective". This introduces a limitation as to the *outcome* of use of the invention. In contrast, the instant claims set forth no such limitation, and read only on the form and components of the composition. Thus, what must be enabled is fundamentally different in the two cases.

Applicants further submit that there is a crucial difference in claiming a "*vaccine for* a pathogenic RNA virus" [emphasis added] and a vaccine composition defined by its components. A "vaccine for" a virus clearly denotes a related outcome with respect to actual or potential infection by the virus. In contrast, the instant claims are defined by the characteristics of the composition, without respect to the outcome of administration.

In view of the above, Applicants respectfully disagree with the Office Action's statement that "the claimed invention is amendable to that of *In re Wright*".

Accordingly, in view of all of the above, Applicants respectfully request that Examiner withdraw the rejections under 35 U.S.C. §112, first paragraph.

Rejection of Claims 1-3, 5-6, and 8-11 13 Under 35 U.S.C. §102 (b)

Examiner rejects claims 1-3, 5-6, and 8-11, 35 U.S..C §102 as being anticipated by Burbage et al. The Office Action states that Burbage et al teaches a vaccine composition of the invention, comprising an antigen bearing target and a fusion protein that falls under the claim limitations. Applicants traverse the rejection.

The Office Action states the following: 1) That the first amino acid sequence used by Burbage et al is ricin; 2) that this amino acid sequence is a lectin; and 3) that this amino acid sequence thus comprises a cell surface binding domain.

Applicants respectfully submit that these statements are incorrect. First, Burbage et al teach that their "first task" was to modify the ricin molecule by making three changes in its amino acid sequence, yielding a molecule that was no longer ricin (page 682, first full paragraph). Their goal in doing so was "to eliminate the normal tissue binding sites on [ricin]", i.e. the galactose binding sites that make ricin a lectin. They characterize the resultant molecule as "lectin-deficient ricin" (abstract and *passim*). Thus, Burbage et al went to lengths to employ an amino acid sequence that is not a lectin, i.e. does not comprise a carbohydrate binding moiety. Their goal in doing so was to ensure that the second amino acid sequence, i.e. GM-CSF, was the sole cell surface binding moiety so that it could target the cytoplasmically active toxin moiety ("lectin-deficient ricin") to AML cells, which express the GM-CSF receptor.

Applicants further note that Burbage's extensive efforts to make ricin "lectin-deficient", and therefore ensure that their molecule lack an essential characteristic of the molecules used in the instant invention, actually teaches away from the instant invention and highlights its inventive step.

The Office Action also states that the recitation "vaccine composition" does not further limit the composition. Applicants respectfully submit that the recitation further limits the composition by requiring a formulation for administration to a subject. Furthermore, Burbage et al teaches its molecule solely as a toxin to eliminate AML cells. It does not teach formulation of a fusion protein with cells for administration to a subject. Indeed, the admixtures of cells with a fusion protein taught therein are created solely for the purpose of *in vitro* testing of the molecule. Regardless of whether the recitation further limits the claim, though, the deficiencies discussed above exclude Burbage et al as prior art under 35 USC 102.

Therefore, Applicants respectfully submit that Burbage et al does not anticipate the instant invention, and request that the rejection under 35 U.S.C. §102 be withdrawn.

Examiner also rejects claims 1-2, 5-6, and 9-11 under 35 USC 102 for lack of novelty over Ramshaw et al, U.S. Pat. No. 5,866,131. Examiner asserts that Ramshaw et al teaches a fusion polypeptide comprising a first amino acid sequence that comprises a cell-surface binding

moiety, and a second amino acid sequence that is a ligand for a cell surface polypeptide of a leukocyte. Applicants traverse the rejection.

In fact, Ramshaw et al does not teach a fusion polypeptide at all. Although this reference teaches nucleic acid constructs that encode multiple amino acid sequences, they are expressed as separate molecules, rather than as a fusion polypeptide. This is expressly evident from the drawings of Ramshaw et al, especially Figure 6a. Moreover, the specification clearly states at column 7, lines 6-8, that the hemagglutinin and cytokine were coexpressed from the viral constructs, "but from separate sites in the viral genome." Thus, they are not combined in a fusion polypeptide.

In order to support a rejection under 35 U.S.C. §102, a reference must teach all elements of the claimed invention. Since a fusion polypeptide is an essential element of the claimed invention, and since Ramshaw et al fails to teach a fusion polypeptide, Ramshaw et al. does not anticipate the instant invention under 35 U.S.C. §102.

The Office Action also states that the recitation "vaccine composition" does not further limit the composition. Applicants respectfully submit that the recitation further limits the composition by requiring a formulation for administration to a subject. Regardless of whether the recitation further limits the claim, though, the deficiencies discussed above should obviate the rejection.

Rejection of Claim 7 Under 35 U.S.C. §103

Examiner rejects claim 7 under 35 U.S.C. §103 as being obvious over Burbage et al in view of Galili et al. Applicant traverses the rejection.

The Office Action states the following: 1) That the first amino acid sequence used by Burbage et al is ricin; 2) that this amino acid sequence is a lectin; and 3) that this amino acid sequence thus comprises a cell-surface binding moiety.

Applicants respectfully submit that these statements are incorrect. First, Burbage et al teach that their "first task" was to modify the ricin molecule by making three changes in its

amino acid sequence, yielding a molecule that was no longer ricin (page 682, first full paragraph). Their goal in doing so was "to eliminate the normal tissue binding sites on [ricin]", i.e. the galactose binding sites that make ricin a lectin. They characterize the resultant molecule as "lectin-deficient ricin" (abstract and *passim*). Thus, Burbage et al went to lengths to employ an amino acid sequence that is not a lectin, i.e. does not cell-surface binding moiety. Their goal in doing so was to ensure that the second amino acid sequence, i.e. GM-CSF, was the sole cell surface binding moiety so that it could target the cytoplasmically active toxin moiety ("lectin-deficient ricin") to AML cells, which express the GM-CSF receptor.

Applicants further note that Burbage's extensive efforts to make ricin "lectin-deficient", and therefore ensure that their molecule lack an essential characteristic of the molecules used in the instant invention, actually teaches away from the instant invention and highlights its inventive step.

Galili et al teaches the administration of tumor cells to elicit an antitumor immune response. However, this reference does not teach administration of a multifunctional molecule as is taught in the instant invention.

Therefore, even if the teachings of the references are combined, they do not provide the essential elements of the instant invention.

Furthermore, Burbage et al teaches its molecule solely as a toxin to eliminate AML cells. It does not teach the ability of the molecule to modulate any immune response when administered in a composition with a cell. These forms of cancer treatment are disparate. Accordingly, there was no motivation to combine these references and, as set forth above, even if combined they do not lead to the instant invention.

Accordingly, in view of the above, Applicants request that all rejections under 35 U.S.C. §103 be withdrawn.

Double Patenting

The Office Action states that the instant claims are rejected under the judicially created doctrine of obviousness type double patenting in view of several co-pending applications. Upon notification of allowable subject matter in the instant case, Applicants will timely file a terminal disclaimer effective to obviate the double patenting rejection.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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